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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/323,765
Filing Date: June 01, 1999
Appellant(s): SCOTT ET AL.

Mark A. Litman
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 23, 2008 appealing from the Office action mailed May 6, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct. The after-final amendment filed on August 1, 2005 has been entered.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,578,442	DESAI et al	11-1996
WO 95/06058	FRANCIS et al	3-1995

Lin, S.-Y and Riggs, A.D.: Photochemical Attachment of lac Repressor to Bromodeoxyuridine-Substitued lac Operator by Ultraviolet Radiation" Proceedings of the National Academy of Sciences U.S.A., vol. 71, no. 3 (March 1974), pp. 947-951.

-Appellant's notation on page 18 of the Brief regarding any Lin et al (1976) reference should be ignored, because it only confuses the record.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(i) Claims 2-7, 18-21, 22-25, 28 & 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Desai et al. (U.S. Patent 5,578,442), *in light of* Lin et al. *(1974).*

Desai et al. teach non-immunogenic cell compositions, as well as methods to produce these compositions, in which non-ionic water soluble polymers (i.e., hydrophilic/ biocompatible; column 4, lines 15-31 & 40-54) are covalently attached to viable, *nucleated*, mammalian cells/tissue through free radical polymerization (i.e., column 4, lines 40-54; column 5, lines 13-26; as it relates to claims 2, 6-7, 18 & 24-25), in which substances, such as polysaccharides (e.g., dextran; as it relates to claim 10) or the polyalkylene glycol, PEG (i.e., as it relates to claim 8), are inherently not toxic (i.e., column 4, lines 15-31; as it relates to claims 3 & 5), and in which attachment to antigenic determinants, as recited, inherently occurs, because any accessible site for attachment also constitutes a putative antigenic site, as does the property that these cells remain viable/survive for over 96 hours, especially when using the same masking/blocking group as claimed (i.e., as it relates to claim 2). In that no "by-products" from the free radical polymerization (and especially as it relates to UV-crosslinking; column 3, lines 57-61) reasonably exist or remain after washing the treated cells to remove non-reacted hydrophilic polymers, the limitations of claim 4 are met. In that free radical/covalent attachment of polycationic/anionic linkage species are also disclosed (e.g., columns 4-5 for polycationic species; column 5-6 for anionic species), the limitations of claims 7 & 24-25 are met. Finally, nucleated cell compositions, and methods of producing such, include islets (i.e., as it relates to claim 22), hepatocytes and neuronal cells (column 5, lines 27-33; as it relates to claims 20-21 & 31), "secreting cells" (i.e., vascular endothelial cells; as it relates to claims 22 & 19), as well as the epithelial cells contained in Desai's "cells having a modified surface" (i.e., column 4, line 47; column 5, lines 27-37; as it relates to claim 23), which are further normally "part of a tissue or organ'" (i.e., as it relates to claim 28), and are reasonably alive (i.e., as it relates to claims 2-7 &

24). It is noted that any reaction with cyanuric chloride (i.e., as recited in claims 18, 28 & 31) would not reasonably change the free radical and/or UV-crosslinking covalent bonds formed, because covalent bonds are covalent bonds, because cyanuric chloride is not required for formation of all covalent bonds, and because these claims are directed to products (i.e., a cellular composition), in which use of cyanuric chloride becomes a product-by-process limitation (i.e., as it relates only to claims 18, 28 & 31).

Accordingly, the courts have held that if the product (i.e., a non-immunogenic cellular composition here) in a product-by-process claim (i.e., as it relates to using cyanuric chloride) is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process. *In re Thorpe,* 227 USPQ 964, 966 (Fed. Cir. 1985): *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983).

This rejection is also consistent with that held by the courts in *Ex parte Gray,* 10 USPQ 2d 1922 (1989); *In re Best,* 195 USPQ 430 (CCPA 1976), which held that:

"the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Accordingly, since the issue in the present appeal is whether the prior art factor is identified or patently indistinct from that of the material on appeal, appellants have the burden of showing that inherency is not involved". *Ex parte Gray,* 10 USPQ 2d 1922 (1989); *In re Best,* 195 USPQ 430 (CCPA 1976).

Likewise, the courts have held that when the prior art product reasonably appears to be the same as that claimed, but differs by process in which it is produced, a rejection of this nature is eminently fair and the burden is upon the appellants to prove, by comparative evidence, a patentable difference (*In re Brown*, 173 USPQ 685 (1972)).

Note that Lin et al is referenced in this rejection solely to establish that it is well known in the art that UV-crosslinking forms *covalent bonds* (e.g., page 947, 1st column) between any

molecule, including proteins, PEG, polysaccharaides, etc. Appellant's attempt to argue on page 19 of the Brief that UV-crosslinking occurs only between protein and DNA only confuses the record and the fact that UV crosslinking can form covalent bonds between any polymer and protein, etc.; consistent with the teachings of Desai et al.

(ii) Claims 1, 4, 8, 10-16, 24 & 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Francis et al. (WO 95/06058).

Francis et al. teach non-aggregating, non-immunogenic, *anuclear* and viable mammalian erythrocyte compositions (i.e., red blood cells) through covalent attachment of the methoxy polyalkylene glycol, TMPEG, as well as methods to produce these compositions (pages 64-65, Example 7; as it relates to claims 1, 8, 13-16, 24 & 26), in which polyalkylene glycols are not toxic at the concentrations used (pages. 14 & 52), as evidenced by no disruption of the cell membrane (i.e. pages 64-65), and in which no "by-products'" from the covalent attachment of PEG reasonably exist or remain after washing the treated cells to remove non-reacted PEG moieties, etc. (i.e., as it relates to claim 4). However, importantly, Francis also teach that covalent attachment of other polymers, such as dextran and ficoll (page 33; as it relates to claims 10-11) and arabinogalactan (page 32; as it relates to claim 12) can be used to improve pharmacological properties of target molecules (pages 14 & 52). Note that none of these claims recite the argued limitation of "at least 25% by number of *nuclear* cells in said composition remain viable for 96 hours…" (i.e., as it relates to non-rejected claim 2 here).

Accordingly, the courts have held that if the product (i.e., a non-immunogenic cellular composition here) in a product-by-process claim (i.e., as it relates to using cyanuric chloride) is

the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process. *In re Thorpe,* 227 USPQ 964, 966 (Fed. Cir. 1985): *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983).

This rejection is also consistent with that held by the courts in *Ex parte Gray,* 10 USPQ 2d 1922 (1989); *In re Best,* 195 USPQ 430 (CCPA 1976), which held that:

"the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Accordingly, since the issue in the present appeal is whether the prior art factor is identified or patently indistinct from that of the material on appeal, appellants have the burden of showing that inherency is not involved". *Ex parte Gray,* 10 USPQ 2d 1922 (1989); *In re Best,* 195 USPQ 430 (CCPA 1976).

Likewise, the courts have held that when the prior art product reasonably appears to be the same as that claimed, but differs by process in which it is produced, a rejection of this nature is eminently fair and the burden is upon the appellants to prove, by comparative evidence, a patentable difference (*In re Brown*, 173 USPQ 685 (1972)).

(iii) Claims 1-26, 28 & 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al., ***in light of*** *Lin et al. (1974),* and in view of Francis et al. (WO 95/06058).

Desai et al. is as set forth above for claims 2-7, 18-21, 22-25, 28 & 31. However, Desai do not specifically disclose non-immunogenic cellular compositions comprising *anuclear* cells/red blood cells, or methods of producing such.

Francis et al. is as set forth above for claims 1, 4, 8, 10-16, 24 & 26. However, Francis et al do not teach covalent attachment of other PEG derivatives, or other polymers, to *nuclear* cell surfaces.

It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to include Francis' red blood cells (RBCs), and alternate methods of covalently attaching other non-immunological polymers to cells (i.e., including any generic methoxy-polyalkylene glycols (mPEG)), as implicitly suggested by Francis (with the exception of the TmPEG species, based solely on the unexpected results within the instant specification; as it relates to claim 9), in Desai's non-immunological cell compositions, because of the common problems of immunorejection of non-compatible antigenic sites between different species/individuals for both *nuclear* and *anuclear* cells (i.e., RBCs and platelets), especially if such tissue/blood is scarce, and because Desai et al. disclose in their Detailed Description of the Invention that "[t]he process of the present invention can be used for rendering non-immunogenic *any* cell, tissue, organ, or system of organs, and the like, that may be used for transplant or the like [emphasis added]" (column 6, lines 15-18; as it relates to claim 28); thereby, providing the motivation for using any cell type, including RBCs , platelets, lymphocytes, and vascular endothelial cells, pancreatic cells and epithelial cells (i.e., as it relates especially to claims 15-16, 17, 18, 19, 20-21, 22, 23, 26 & 28) as a substrate for making non-immunogenic cell compositions.

Accordingly, it has been held by the Supreme Court in KSR International Co. v. Teleflex Inc. et al (82 USPQ2d 1385 (2007)) that a simple substitution of one known, equivalent element [i.e., use of free radical polymerization or UV cross-linking versus use of cyanuric chloride to form covalent bonds; or use of Francis' masking/blocking groups, PEG, mPEG, dextran, ficoll and/or arabinogalactan] for another to obtain predictable results [i.e., formation of covalent linkages of masking/bolcking compounds to cells to make them non-immunogenic], or the

combining of prior art elements according to known methods [of forming covalent bonds] to yield predictable results [i.e., form stable covalent linkages between known masking/blocking compounds/groups and cells to make them non-immunogenic], reasonably supports a *prima facie* case of obviousness, especially given a finite number of predictable solutions [i.e., a non-immunogenic viable cellular composition] where it would be obvious to try based on the teachings of Desai et al. or Francis et al.

(10) Response to Argument

(i) In summary, the invention is directed to masking/blocking normal immunological determinants/ antigens on either *anuclear* or *nuclear* cells using compounds such as polyethylene glycol (PEG), dextran, polysaccharides, etc., in order to minimize immunorejection of administered foreign cells. The instant invention is directed to making covalent bonds between the masking/blocking compounds (e.g., PEG), and the foreign cells. Appellants' arguments address only Desai's teachings using ionic bonds, instead of Desai's teachings of using covalent bonds, to form the linkages between the masking/blocking compounds (e.g., PEG) and the foreign cells to be eventually administered. Unfortunately, Appellants also misstate claim limitations (e.g., see page 25 of the Brief), and presents arguments for claims not rejected under 35 U.S.C. 102(e) or (b); thereby, potentially confusing the actual issues on appeal. For example, Claim 4 dos not recite "absence of toxic-bye products..." (see page 25 of the Brief). Additionally, neither claims 10 & 16, nor claim 18 recite the product-by-process limitation of using cyanuric chloride. Claim 11 is further not rejected under 35 U.S.C. 102 (e) by Desai, and

Francis does specifically teach use of the masking/blocking groups, ficoll and arabinogalactan on pages 33 and 32, respectively, as presented in the rejection above.

The Examiner's position is consistent with MPEP 2123, which states that "patents are relevant as prior art for all they contain", and that "nonpreferred embodiments constitute prior art". In other words, Desai clearly teach "covalent bonding" through, for example, free radical polymerization (i.e., col. 4, lines 40-54; col. 5, lines 13-26), and through UV-crosslinking (e.g., col. 3, lines 57-61), and as supported by Desai's statement that "[i]*n addition, the* ***further*** *crosslinking of the graft polymer forms a highly stabilized* [i.e., covalent binding], immuno-protective coating of water-soluble [i.e., hydrophilic, by definition] polymer about the treated cell or tissue" [emphasis added], therefore at antigenic sites which are present in throughout all membrane-bounded proteins, by definition (column 3, lines 53-56). As further support, it is well known in the art that UV-crosslinking constitutes formation of covalent bonds, wherein Lin et al. is solely referenced in this rejection for the teaching that UV-crosslinking forms **covalent bonds** (e.g., page 947, 1st column). Thus, Appellants' arguments concerning other embodiments taught by Desai (e.g., ionic bonds), or tangential and hyperbolic arguments that "if the listed acids [which are not part of the rejection] were capable of inherently forming covalent bonds with cells and tissues (in the absence of enzymes or catalysts for that specific reaction), life as we know it would cease on Earth", only cloud the issue of whether covalent bond formation using UV crosslinking or free radical formation is an equivalent element for obtaining predictable results of linking masking/blocking compounds (e.g., such as PEG) to cells in order to make them non-immunogenic. Arguments on page 17 concerning "free radical polymerization… refer[s] to free radical polymerization of components in the compostion to each other, and there is no free

radical polymerization to a cell…" make little sense, appear to be merely based upon supposition, and therefore, should not be found persuasive by the Board. Finally, arguments referring to pages 27-32 of the specification are further taken out of context, in which covalent bonds are covalent bonds, versus "milder covalent bonds" (see page 17 of the Brief), and where arguments concerning the teachings of Francis et al. are also not on point with this particular rejection, and therefore, will be discussed below as they more accurately relate to the art rejection over Francis et al. in rejection # (ii). In summary, arguments related to other embodiments (e.g., formation solely of ionic bonds, even if such are preferred embodiments within the patent) should not be found persuasive by the Board, because this other preferred teaching within Desai et al. is not part of this pending rejection.

Thus, the rejection of record clearly establishes a *prima facie* case for anticipation because Desai's polycationic species are clearly "hydrophilic ["water-soluble"], biocompatible, [and] non-immunogenicity providing compound or polymer", form "highly stabilized" covalent bonds with membrane-bounded proteins (i.e., antigenic sites, by definition) after free radical-induced or UV-induced crosslinking of any of Desai's previously made ionic linkage groups (which Lin et al teach results in covalent bond formation), and because the instant rejection is consistent with that held by the court in *Ex parte Gray, In re Best, In re Brown*, *In re Thorpe,* and *In re Marosi*.

It is again noted that Lin et al is referenced in this rejection to establish that it is well known in the art that UV-crosslinking forms covalent bonds (e.g., page 947, 1st column).

(ii) Note that Appellants acknowledged on page 20 of the Brief that "Francis does apparently incidentally show the covalent bonding of a moiety (including PEG, the erythrocytes of Example 7) to the surface of a red blood cell...", but is done for a different purpose, which alternatively and inherently supports the rejection made of record for these claims. Thus, whatever Francis' intent may have been, or not, is immaterial to whether Francis teach the broadly claimed products in this 102 rejection. In addition, Appellants' arguments to limitations not recited in the claims should be further ignored by the Board. For example, inherent properties (i.e., "an anti-immunogenic effect") are inherent whether they are recognized by a reference, or not, and where "motivation" is a consideration under 35 U.S.C. 103, and not 35 U.S.C. 102. It is further noted that any unexpected results for using one species of blocking group that is related to the degree of anti-immunogenic effect, as assayed within the instant specification (e.g., Example IX; pages 27-32) should not be found to obviate a rejection under 35 U.S.C. 102, because Francis also teach use of other structural masking/blocking compounds, as also recited in the instant claims (i.e., compounds besides the TmPEG species) to make their non-immunogenic cell products, and because only claim 9 [which is not part of this particular rejection for "anuclear cells"] recites use of a generic methoxy-polyalkylene glycol (e.g., which includes the TmPEG species with its unexpected results) versus the CmPEG species (i.e., also a methoxy-polyalkylene glycol). It is again emphasized that only TmPEG has been disclosed within the specification to exhibit "no immunological modification" to RBCs (see page 30 of the instant specification). In other words, arguments directed to claim limitations in claim 9, which is not part of this rejection over Francis et al., should be found moot.

(iii) The instant rejection should not stand or fall solely on the teachings of Francis et al., especially in light of the further evidence provided by the Examiner concerning the teachings of Lin et al.; which remains consistent with that held by the court in KSR International Co. v. Teleflex Inc. et al., as discussed above.

The teachings of Desai et al., *in light of Lin et al*., and in view of Francis et al., clearly give rise to non-immunogenic cells by virtue of the intrinsic properties of the cells made by Desai et al., in view of Francis et al., which would be non-immunogenic, by definition, due to the masking/blocking groups taught by both Desai et al. and Francis et al. In other words, Appellants' arguments regarding use of the sole species, TmPEG (which is also broadly encompassed by Appellants' claim 9), and "the specific degree of viability" (i.e., which is recited in only claim 2) does not accurately address the actual rejection made of record, and therefore, should be not be found persuasive by the Board.

Appellants' acknowledgement that "Francis does apparently incidentally show the covalent bonding of a moiety (including PEG, the erythrocytes of Example 7) to the surface of a red blood cell...", but is done for a different purpose, should further support this *prima facie* obviousness rejection.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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